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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,057	07/06/2001	Fayad Z. Sheabar	4532660/29930	7817

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EXAMINER	
LEITH, PATRICIA A	
ART UNIT	**PAPER NUMBER**
1655	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/900,057	SHEABAR ET AL.	
	Examiner	Art Unit	
	Patricia Leith	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 and 10-18 remain pending in the application and were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office Action.

Terminal Disclaimer

The terminal disclaimer filed on 9/5/06 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US patent No. 6,767,566 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

Claims 1-7 and 10-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Upon further careful consideration, it is deemed that the claims are indefinite for the following reasons:

Claims 1, 17 and 18 all recite 'without substantially denaturing'. This phrase is deemed indefinite in that the metes and bounds of the claim language cannot be fully understood. 'Substantially denaturing' is not specifically defined in the Specification. The method links the temperature as claimed to the degree of denaturing of the potato II protease inhibitor. One of ordinary skill in the art would not know if they were in possession of such a method because of the ambiguity of the phrase 'without substantially denaturing'. How much can the protein be denatured and still meet the limitations of the claim? Clarification is necessary.

Claims 1, 17 and 18 all also recite 'to selectively affect the purity and yield'. This statement is deemed indefinite in that one of ordinary skill in the art would not know if they were in possession of the method with regard to the temperatures as recited in the claims. The phrase 'to selectively affect' refers to (is linked to) specific temperatures, but the Examiner is not sure what these temperatures are. It appears that the temperatures are any temperatures, since the claim does not state *how the purity is affected* but the Examiner cannot be absolutely sure. Correction is necessary.

Claims 1, 17 and 18 also recite 'removing denatured protein products'. This phrase lacks clear antecedent basis in the respective claims. It is not understood

completely if the potato proteinase inhibitor II is removed, since the claim stated that the inhibitor may be partially denatured. If the proteinase inhibitor II is partially denatured, is it considered a denatured protein? If so, what is left to purify? Therefore, it is not known if the potato proteinase inhibitor II is also included in this phrase.

Because the remainder of the claims; i.e., claims 2-7 and 10-16 are dependant upon claim 1, claims 2-7 and 10-16 necessarily possess all of the limitations of claim 1. Because claims 2-7 and 10-16 do not remedy the indefiniteness of claim 1, these claims are also properly rejected under this statute for being indefinite.

Claim Rejections - 35 USC § 102

Claims 1, 2, 3, 4, 10, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Ryan et al. (WO 99/01474) *in light of* Pearce et al. (1983)* and Bryant et al. (1976)* and Borud (EP 0487480 A2)*. Upon further consideration, it is deemed that Ryan et al. anticipates the claimed invention.

Ryan et al. (WO 99/01474) taught a method for isolating proteinase inhibitor II from potato tubers via extraction with a mixture of solvents (water/ethanol/.88% formic acid and 1.5 M NaCl), filtration via cheesecloth, heating the liquid portion to 70 C, cooling, evaporation of ethanol, centrifugation and ultrafiltration via dialysis with 12-14 kD MW cutoff (p.9,. Example 1 and claims 1-6). Ryan et al. taught that the precipitated

proteins were advantageously dissolved in 0.1 M ammonium bicarbonate (p.8, lines 25-26). Ryan et al. mentioned that the addition of ammonium bicarbonate was 'suitable for solubilization and subsequent lyophilization - *a known method for stable storage of protease inhibitors*' (p.8, lines 25-27, emphasis added).

While the claims state 'preparing a mixture of an alcohol-free solvent...' the method claim also states 'comprising the steps of' which is open language. Ryan et al. clearly incorporated water into the extraction mixture which is an 'alcohol-free solvent'. A suggestion to overcome this rejection is to amend the claim to read: 'by preparing a mixture of an organic acid selected...., and comminuted potato tubers to form a solid fraction and a liquid fraction...and other protein products, wherein said extraction is carried out in the absence of alcohol'.

It is deemed that heating the mixture to 70 °C would have denatured some of the proteins but not the potato proteinase inhibitor II in light of the following references:

Pearce et a. (1983) taught that carboxypeptidase inhibitors from potato tubers were heat stable ***to*** 80 °C (p.223, col.2, 'Results and Discussion').

Bryant et al. (1976) taught that proteinase inhibitor II (trypsin/chymotrypsin inhibitor) from potatoes was heat stable ***at*** 80 °C (p. 3419, col.2 'Isolation of Proteinase inhibitor II).

Borud (EP 0487480 A2) taught that purification of potato proteinase inhibitor II was effected by heating to 65 °C to denature unwanted proteins while rendering the proteinase inhibitor II stable.

Therefore, because Ryan et al. heated the potato slurry to 70 °C, it is deemed that they concurrently heated the liquid fraction to a 'temperature and for a time period sufficient to denature at least some of the other protein products without substantially denaturing the potato proteinase inhibitor II and adjusted the temperature and time period of the heat treatment step to selectively affect the purity and yield of the potato proteinase inhibitor II. Ryan et al. clearly removed the denatured proteins via ultrafiltration.

* These references are cited merely to relay an inherent property of heating a potato slurry to 70 °C and are not used in the basis for rejection *per se.*

Claim Rejections - 35 USC § 103

Claims 1-7 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan et al. (WO 99/01474) in view of Borud (EP 0487480 A2) in view of Pearce et al. (1983) in view of Bryant et al. (1976).

The teachings of Ryan et al. were discussed *supra*. Ryan did not specifically teach wherein the heat step was conducted between about 30 min. to about 180 min, or wherein the heating step was conducted at a temperature greater than about 75 °C or wherein ammonium bicarbonate was specifically added during filtration, wherein the clarified extract was concentrated to less than one-fifth of the starting volume, or wherein filtration comprised washing the extract with up to ten volumes of filtration buffer.

Borud (EP 0487480 A2) disclosed a method for purification of a proteinase inhibitor which comprised separation of potato solids from the water-soluble liquid via high speed grating and sieving or centrifuging (col.3, lines 7-33). A summary of small - scale production of the proteinase inhibitors was discussed on col.5, lines 33-49: Hydrochloric acid (solvent) was added to the liquid potato extract to bring the pH to about 4.4 (col.5, lines 3-4 and lines 44-45). Proteins were coagulated by heating for 20 minutes at 65 °C followed by cooling to 20 C (col.5, lines 45-48).

The coagulated (precipitated) proteins were removed via filtration (col.5, lines 48-49), and the remaining liquid (clarified extract solution) was concentrated via ultrafiltration with a DDS-FILTRATION equipment which employed a polysulfone membrane with an average pore size of 10 /, MW cut off of about 10 kD (10 / approximately equals 0.01 μm) (col.6, lines 25-29). The flux of the retentate was

reported at 70 L permeate/m^2/h (col.6, line 29) which approximately equals .11 L/ft^2/min (1 m^2 = 10.76 ft^2). Thus, it was clear from Borud that a membrane with a molecular weight cut-off with 10 kD (within the Instantly claimed range) would have allowed lower molecular weight molecules to traverse the membrane, while the protease inhibitors were forced back through into the retentate solution.

It is deemed that Borud heated the liquid fraction to a time sufficient to denature at least some of the other protein products without substantially denaturing the protease inhibitor because, as clearly indicated by Borud, "The process which is described here, aim[s] at extracting and concentrating the reasonably [heat-stable] inhibitors from the [potato-juice]" (col.4, lines 28-30). Here, Borud is referring to the 3 types of protease inhibitors as indicated at col.4, lines 22-27 which include chymotripsin inhibitors, chymotripsin and trypsin inhibitors and carboxypeptidase A and B inhibitors. Further, Borud states "After coagulation and removal of inactive proteins.." (col. 5, lines 53-54). Thus, it is clear that the goal of Borud was to heat the potato slurry (containing solids and liquids) to a temperature which would denature and precipitate unwanted proteins, but leave the proteins as described at col.4, lines 22-27. Here, Borud 'adjusted the temperature and time period of the heat treatment to selectively affect the purity and yield of the protease inhibitor' especially as evidenced by the statement "The heating to coagulation temperature is done continuously in a tube [heat exchanger] dimensioned for little over temperatures on the heat-transporting surfaces to avoid local overheating

which may destroy inhibitor proteins" (col.5, lines 10-13) and further gave a specific time range and temperature range in which to carry out the extraction as stated *supra*.

Absent any definition of the phrase 'about 30', it is deemed that 20 minutes is 'about 30 minutes'. Further, Borud clearly taught that the precipitate collected after coagulation (heating) was separated via decantercentrifuge (col.3, line 55-col.4 line 2).

Pearce et a. (1983) taught that carboxypeptidase inhibitors from potato tubers were heat stable ***to*** 80 °C (p.223, col.2, 'Results and Discussion').

Bryant et al. (1976) taught that proteinase inhibitor II (trypsin/chymotrypsin inhibitor) from potatoes was heat stable ***at*** 80 °C (p. 3419, col.2 'Isolation of Proteinase inhibitor II).

One of ordinary skill in the art would have been motivated to heat the potato slurry between about 30 to about 180 minutes because heating for this length of time would have permitted a substantial amount of proteins to be denatured, but would not affect the potato proteinase inhibitor II. It is clear that it is the temperature which denatures the proteins, and not the length of time which the protein is subjected to the heat treatment. One of ordinary skill in the art would have had a reasonable

expectation that heating to 70 °C for say, 30 minutes instead of say 2 minutes would have more completely degraded the non-target proteins.

One of ordinary skill in the art would have been motivated to have heated the protein slurry to greater than about 75 °C in order to have purified either carboxypeptidase inhibitor or proteinase inhibitor II. It was clear from Pearce et al. as well as Bryant et al. that both of these particular proteases were heat stable at 80 °C and therefore, the ordinary artisan would have had a good expectation that heating to 80 °C would have heat denatured many other proteins while saving these proteinase inhibitors.

One of ordinary skill in the art would have been motivated to have concentrated the volume of the liquid protein slurry to 1/5 of the starting volume in order to de-salt the protein mixture in order to prepare the crude mixture for further purification such as column chromatography. The ordinary artisan would have recognized that the salt would need to be removed from solution in order to standardize the conductivity, thereby allowing the proteins to elute from the column based upon their respective ionic strengths.

One of ordinary skill in the art would have been motivated to wash the final protein product to remove any unwanted contaminants. Washing proteins with storage

buffer was old and well known in the art of protein purification, as well as other forms of purification. The ordinary artisan would have had a reasonable expectation that washing the final protein precipitate would have 'cleaned-up' the protease, thereby creating a protease with greater activity as well as better stability upon storage.

One of ordinary skill in the art would have been motivated to add ammonium bicarbonate buffer prior to filtration in order to stabilize the protein thereby affecting a greater overall yield.

One of ordinary skill in the art would have been motivated to wash the final protein product to remove any unwanted contaminants. Washing proteins with storage buffer was old and well known in the art of protein purification, as well as other forms of purification. The ordinary artisan would have had a reasonable expectation that washing the final protein precipitate would have 'cleaned-up' the protease, thereby creating a protease with greater activity as well as better stability upon storage.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patricia Leith
Primary Examiner
Art Unit 1655

April 9, 2007